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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,399	02/11/2005	Andreas Krause	TX/4-32608A	6111

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
11/18/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,399	KRAUSE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,8-11 and 15-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8-11 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 7/24/2009, in which claims 1, 3, 11 and 16-18 were amended. Claims 1-3, 8-11 and 15-18 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected Group I without traverse in the reply filed 11/14/2008. Claims 1-3, 8-11 and 15-18 are under consideration.

Specification

The use of the trademarks GENBANK (paragraph bridging pages 1-2), RNEASY (page 10 under the section titled "RNA amplification), and RIBOGREEN (page 10 under the section titled "RNA amplification") has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Response to Arguments - Specification

With respect to the objection to the specification, Applicant's arguments filed 7/24/2009 have been fully considered but they are not persuasive. The response asserts that Applicants have amended the specification to capitalize trademarks. While most trademarks have been capitalized by the amendment, the use of the trademarks GENBANK (paragraph bridging pages 1-2, see especially page 2, line 1), and the trademarks RNEASY and RIBOGREEN at page 10 under the section titled "RNA amplification" has not been corrected by the amendment. For these reasons, the objection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 8-11 and 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was made in the Office action mailed 6/19/2009 but has been rewritten to address the amendments to the claims in the reply filed 7/24/2009.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of

experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claims 1, 2, 8-11, 15 and 16 are drawn to a method of early diagnosing chronic rejection (CR) in a kidney transplanted subject. Claim 1 sets forth the method steps of (a) assaying as a baseline value the levels of expression of the nucleic acid sequences set forth in SEQ ID NOs: 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38 (hereinafter referred to as SEQ ID NOs: 29-38), mRNA transcribed therefrom or protein encoded thereby in a renal allograft tissue biopsy obtained from a kidney transplanted control subject who is known not to develop CR; (b) assaying as a test value the levels of expression of the nucleic acid sequences set forth in SEQ ID NOs: 29-38, mRNA transcribed therefrom or protein encoded thereby in a renal allograft tissue biopsy obtained from a kidney transplanted test subject within the first year post-transplantation; and (c) comparing the baseline value of step (a) with the test value of step (b), wherein a baseline value lower than the test value, in the case of the levels of expression of the nucleic acid sequences set forth in SEQ ID NO: 29, 30, 31, 32, 33, 34, 35 or 36, mRNA transcribed therefrom or protein encoded thereby and higher than the test value, in the case of the levels of expression of the nucleic acid sequences set forth in SEQ ID NO: 37 or 38, mRNA transcribed therefrom or protein encoded thereby predicts that the kidney transplanted test subject has an increased risk of developing CR. Claim 2 limits the method to where the renal allograft tissue biopsy of the transplanted control subject is obtained from the control subject at the day of transplantation. Claims 8 and 9 limit the method to the detection of protein encoded by the nucleic acid sequences. Claims 10 and 11 limit the method to the detection of mRNA expression. Claim 15 limits the method to where the renal allograft tissue

biopsy obtained from the kidney transplanted test subject in step (b) is obtained within 4-7 months post-transplantation. Claim 16 limits the method to where the renal allograft tissue biopsy obtained from the kidney transplanted test subject in step (b) is obtained around 6 months post-transplantation.

Claims 3, 17 and 18 are drawn to a method for monitoring in a kidney transplanted subject at risk of developing CR, comprising the steps of (a) assaying the levels of expression of the nucleic acid sequences set forth in SEQ ID NOs: 29-38, mRNA transcribed therefrom or protein encoded thereby in a renal allograft tissue biopsy sample obtained from a kidney transplanted subject prior to exposure to transplant therapy; (b) assaying the levels of expression of the nucleic acid sequences set forth in SEQ ID NOs: 29-38, mRNA transcribed therefrom or protein encoded thereby in at least one renal allograft tissue biopsy sample obtained from the kidney transplanted subject after exposure to transplant therapy; and (c) comparing the levels of expression detected in step (a) and step (b), wherein an increase in the levels detected in step (b) in comparison to the levels detected in step (a) in the case of the nucleic acid sequences set forth in SEQ ID NOs; 29, 30, 31, 32, 33, 34, 35 and 36, mRNA transcribed therefrom or protein encoded thereby and a decrease in the levels detected in step (b) in comparison to the levels detected in step (a) in the case of the levels of expression of the nucleic acid sequences set forth in SEQ ID NO: 37 and 38, mRNA transcribed therefrom or protein encoded thereby indicates an increased likelihood of developing CR.

The nature of the invention is complex in that one must be capable of determining the level of mRNA transcribed from each of the recited sequences and the level of protein encoded by each of the recited sequences. Moreover, the sequence of SEQ ID NO; 36 is mostly

composed of undefined residues, which may be a, c, g or t. Thus, one would not know what protein is encoded by the sequence.

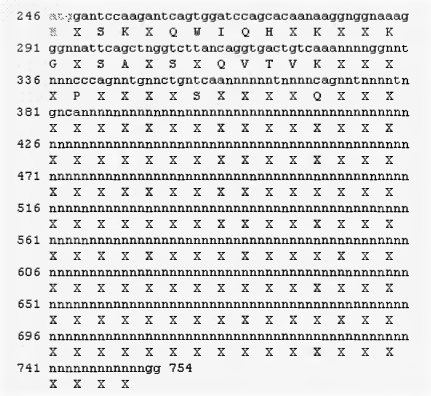
Breadth of the claims: The claims are specifically drawn to the measurement of expression of the nucleic acid sequences of SEQ ID NOs: 29-38, mRNA transcribed therefrom or protein encoded thereby.

Guidance of the specification and existence of working examples: The specification teaches the study of gene expression as part of a randomized, multicenter, double-blind, double-dummy, parallel group study in which serial renal protocol biopsies were taken at the time of transplantation (baseline), then 6 months and 12 months after transplantation (e.g., page 9, 1st full paragraph). The specification provides guidance with regard to the isolation of mRNA from the renal allograft tissue biopsies obtained from the kidney transplanted subjects and processing of the mRNA samples for hybridization to an Affymetrix oligonucleotide array (e.g., pages 9-14). To measure gene expression in the renal allograft tissue biopsies, processed aRNA was hybridized to an Affymetrix HG U95A v2 chip containing oligonucleotide probes for about 12,000 human genes (e.g., page 9, 2nd full paragraph). Statistical analysis was performed to determine the ability of the gene expression data to distinguish between the subjects who went on to develop CR and those that did not (e.g., pages 15-16). The specification teaches the use of the t and Wilcoxon statistics and the statistical measure described at page 15 to identify the genes that separate best the chronic rejection group from the control group (e.g., page 17, 1st paragraph). Applying the measures to each gene individually delivered a measure for the separation of the two groups, where the Q20/80 method identified 65 genes and the Q15/85 method identified 16 genes with complete separation of the (20%, 80%) and (15%, 85%)

quantile ranges, respectively (e.g., page 17, 1st paragraph). Next, those genes were compared to the genes detected by the t- and Wilcoxon statistic, leading to the identification of 10 genes, which ranked among the 100 with most extreme t- and Wilcoxon statistic (e.g., page 17). Those gene identifiers and annotations are shown in Table 3. Using the Pearson Correlation, the set of 65 genes separates the two patient groups perfectly (e.g., page 18). When the set of 10 genes was used, RNA expression profiles predicted the occurrence/non-occurrence of chronic rejection in 15 out of 17 patients (>88%) (e.g., page 18, last paragraph). Further, the set of 10 genes was also able to predict that a 12 month biopsy belonged to a patient that developed CR at month 18 (e.g., page 18, last paragraph). Accordingly, when the Affymetrix HG U95A v2 chip is used to measure RNA expression for the 10 genes recited in Table 3, the method is predictive for chronic rejection. However, the claimed method requires measuring the expression level of mRNA transcribed from SEQ ID NO: 36 or protein encoded thereby. The specification teaches that there was insufficient sequence data to design TaqMan primers and probe for quantitative RT-PCR (e.g., Table 3).

Predictability and state of the art: It would be unpredictable to practice the claimed invention, because the specification and prior art do not teach one how to measure the mRNA transcribed from SEQ ID NO: 36 or protein encoded thereby. The specification describes the sequence of SEQ ID NO: 36 as GenBank Accession No. W26469, which is an uncharacterized expressed sequence tag (EST) designated 32f4 (e.g., Tables 3 and 6). If oligonucleotide probes were made from the sequence of SEQ ID NO: 36, those probes are likely to hybridize to different genes located on different human chromosomes (see the BLAST result in Appendix I, mailed

6/19/2009). Furthermore, he longest "open reading frame" of the EST encodes a largely undefined protein, which is shown below.



Furthermore, the GenBank record for Accession No. W26469 indicates that the clone for the EST is not available. Thus, one would not be able to determine the expression levels by methods such as Northern blot analysis, reverse transcription PCR, real time quantitative PCR, or Western blot. Moreover, the probe sequences on the Affymetrix array that were capable of detecting differences in expression of the uncharacterized EST of SEQ ID NO: 36 are not taught by the specification.

Amount of experimentation necessary: Given the degenerate nature of the nucleotide sequence of SEQ ID NO: 36, it would require a large amount of experimentation to determine the identity of this sequence in a manner that would in some way enable the claimed invention.

One embodiment of the method encompasses the use of an oligonucleotide array to detect the expression of SEQ ID NO: 36. However, the specification does not disclose the relationship between the probe sequences on the Affymetrix Array used in the specification and the sequence of SEQ ID NO: 36. One would be required to test probes obtained from the sequence of SEQ ID NO: 36 for the ability to assay the expression of a gene, which is predictive for chronic rejection. Given that many different genes are likely to be detected by such probes, this is an unpredictable venture. Another embodiment of the method involves the use of quantitative PCR such as TaqMan. However, the specification teaches that TaqMan analysis was no performed due to the limited sequence information for W26469. Additional experimentation would be required to determine sufficient gene sequence to make and use primers and probes for quantitative detection of mRNA by RT-PCR. Identification of the gene from which the EST of W26469 is transcribed would also be required for any method based upon the analysis of protein encoded by the gene. The specification and prior art do not teach the protein sequence encoded by the gene from which EST ID 32f4 (W26469) is transcribed.

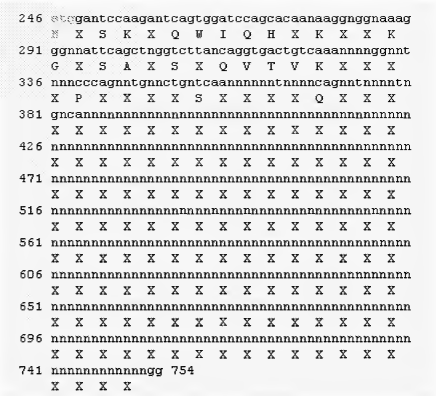
In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1-3, 8-11 and 15-18 are not considered to be enabled by the instant specification.

Claims 1-3, 8-11 and 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was made in the Office action mailed 6/19/2009 but has been rewritten to address the amendments to the claims in the reply filed 7/24/2009.

The claims require the provision of reagents to assay levels of expression of the nucleic acid sequence set forth in SEQ ID NO: 36, mRNA transcribed therefrom, or protein encoded thereby. The rejected claims thus require the description of sequences such that reagents can be designed to assay expression levels for the prediction of chronic rejection.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes the sequence of SEQ ID NOs: 29-38. However, the disclosure of the sequence of SEQ ID NO: 36 is not sufficient to allow one to envision the structure of those reagents that could be used to assay the levels of expression of the gene, which is predictive for chronic allograft rejection. The specification describes the sequence of SEQ ID NO: 36 as GenBank Accession No. W26469, which is an uncharacterized expressed sequence tag (EST) designated 32f4 (e.g., Tables 3 and 6). If oligonucleotide probes were made from the sequence of SEQ ID NO: 36, those probes are likely to hybridize to different genes located on different human chromosomes (see the BLAST result in Appendix I, mailed 6/19/2009). Furthermore, he longest "open reading frame" of the EST encodes a largely undefined protein, which is shown below.



Furthermore, the GenBank record for Accession No. W26469 indicates that the clone for the EST is not available. Thus, one would not be able to determine the expression levels by methods such as Northern blot analysis, reverse transcription PCR, real time quantitative PCR, or Western blot. Moreover, the probe sequences on the Affymetrix array that were capable of detecting differences in expression of the uncharacterized EST of SEQ ID NO: 36 are not taught by the specification.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of corresponding sequences or the full sequence of EST ID 32f4.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry,

whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the sequence from which the reagents are designed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

The sequence of SEQ ID NO: 36 does not provide sufficient detail for one to envision the gene whose expression is predictive of chronic allograft rejection. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 1-3, 8-11 and 15-18.

Response to Arguments - 35 USC § 112

The rejection of claims 17 and 18 under 35 U.S.C. 112, first paragraph (new matter), has been withdrawn in view of Applicant's amendment to the claims in the reply filed 7/24/2009.

With respect to the rejection of claims 1-3, 8-11 and 15-18 are rejected under 35 U.S.C. 112, first paragraph (enablement), Applicant's arguments filed 7/24/2009 have been fully considered but they are not persuasive.

At page 12, paragraph 1, the response asserts that the use of a microarray is readily available to identify the level of expression of SEQ ID NO: 36.

This argument is not found persuasive. As discussed in the rejection of record, the probe sequences on the Affymetrix array that were capable of detecting differences in expression of the uncharacterized EST of SEQ ID NO: 36 are not taught by the specification. If oligonucleotide probes were made from the sequence of SEQ ID NO: 36, those probes are likely to hybridize to different genes located on different human chromosomes (see the BLAST result in Appendix I, mailed 6/19/2009). The specification does not disclose the relationship between the probe sequences on the Affymetrix Array used in the specification and the sequence of SEQ ID NO: 36. One would be required to test probes obtained from the sequence of SEQ ID NO: 36 for the ability to assay the expression of a gene, which is predictive for chronic rejection. Given that many different genes are likely to be detected by such probes, this is an unpredictable venture, which would require undue experimentation.

At page 12, the response states that if one were to assume that microarray technology was was the only method available to measure the level of expression of SEQ ID NO: 36, this fact would not render the claim non-enabled. The response points to MPEP 2164.08, which states that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled, and the standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Further, the response asserts that it is the Office's contention that the specification teaches that Q-PCR was unavailable to identify W26469 (SEQ ID NO: 36), and no undue experimentation would have been necessary to determine that Q-PCR or primer-based techniques are inoperable. The response asserts that it is the Office's contention that there is insufficient sequence information to determine a protein

sequence, and no undue experimentation would be required to determine that antibody detection is inoperative. Thus, the response asserts that one could determine which embodiments that were conceived but not yet made would be inoperable without expenditure of no more effort than is normally required in the art.

These arguments are not found persuasive. For the reasons discussed two paragraphs above, the use of microarray technology to detect the expression of SEQ ID NO: 36 is not operable based upon the teachings of the present specification and prior art. While a generic claim can contain inoperative embodiments, there must be some enabled scope. In the instant case, the claims require assaying the level of expression of the nucleic acid sequence of SEQ ID NO: 36, mRNA transcribed therefrom, or protein encoded thereby. Claim 8 specifically requires measuring the levels of protein encoded by the nucleic acid sequences, and claim 9 requires the levels or protein to be assayed using reagents that specifically bind the proteins. Claim 11 requires assaying levels of mRNA transcribed from the nucleic acid sequence of SEQ ID NO: 36, and claim 10 requires mRNA expression to be assayed by Northern blot analysis, a hybridization technique, reverse transcription PCR, or real time quantitative PCR. These are the same techniques contemplated by the present specification (e.g., page 3, paragraph 1; page 7, paragraphs 1-3). For assaying protein expression, the specification envisions the use of antibodies and formats such as enzyme immunoassay, radioimmunoassay, Western blot analysis and ELISA (e.g., page 7, paragraph 3). Each of the claimed and disclosed methods require the nucleic acid sequence or amino acid sequence to make and use the assay to measure expression levels. Hybridization techniques are not enabled, because the specification does not disclose the relationship between the probe sequences on the Affymetrix Array used in the specification and

the sequence of SEQ ID NO: 36. One would be required to test probes obtained from the sequence of SEQ ID NO: 36 for the ability to assay the expression of a gene, which is predictive for chronic rejection. Given that many different genes are likely to be detected by such probes, this is an unpredictable venture, which would require undue experimentation. The specification teaches that there was insufficient sequence data to design TaqMan primers and probe for quantitative RT-PCR (e.g., Table 3). Thus, primer-based techniques are not enabled. The sequence of the protein encoded by SEQ ID NO: 36 is largely undefined, and no significant open reading frame could be detected (see page 10 of the Office action mailed 6/19/2009). Protein detection for the protein encoded by SEQ ID NO: 36 is not enabled. Accordingly, the claims are directed to embodiments that one could not make and used based upon the teachings of the as-filed disclosure and prior art. Therefore, the claims do not meet the enablement standard.

At the last paragraph of page 12, the response asserts that the EST entry for W26469 from GenBank provides all the guidance required to enable a skilled artisan to identify levels of W26469 using techniques other than microarray technology. At page 13, the response points to the following teachings of the GenBank entry: (1) the library used for sequencing the EST was a sub-library derived from a human retina cDNA library; (2) inserts from the human retina cDNA library were isolated, randomly primed, PCR amplified, size-selected, and cloned into lambda gt10; and (3) individual plaques were arrayed and used as templates for PCR amplification, and, these PCR products were used for sequencing. Further, the response asserts that the GenBank entry also provides the sequences for the forward and backward primers, as well as the sequencing primer, that was used by Dr. Nathans of Johns Hopkins to identify the sequence of EST W26469. The response asserts that the protocol for obtaining a clone for W26469 is

provided by the EST entry, and once a clone is obtained, it is routine experimentation to sequence the clone for providing RT- or Q-PCR primers, or to identify an open reading frame to obtain a protein sequence for the preparation of an antibody.

These arguments are not found persuasive. The instructions provided will identify the sequence of any expressed gene in human retina and do not result in the specific sequence of W26469. The primer sequences provided by Dr. Nathans are not specific to the insert sequence for W26469. Rather, they are sequences common to all expressed sequence tags in the library. Furthermore, the GenBank entry specifically states, "Clones from this library are NOT available" (see the top of page 2). It would require undue experimentation to randomly screen all expressed sequence tags from a human retina cDNA library to identify the sequence of W26469 (i.e., to determine the sequence ambiguities of SEQ ID NO: 36). Furthermore, one could perform each of the steps suggested by Applicant and discover that the EST clone is of only the 5' or 3' untranslated region of a transcript, which does not contain an open reading frame. The type of experimentation required to determine the sequence of SEQ ID NO: 36, mRNA transcribed therefrom, and protein encoded thereby would not be routine and would be undue.

At page 13, the response notes that the Federal Circuit has recently discussed the advancement of molecular biology methods in the context of obviousness in *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009). The response notes that in *Kubin*, the Court found a nucleotide sequence to be obvious because:

> [t]he record shows that the prior art teaches [the existence of] a protein of interest, a motivation to isolate the gene coding for that protein, and illustrative

instructions to use a monoclonal antibody specific to the protein for cloning this gene.

Thus, the response asserts that by knowing the mere existence of a protein coupled with routine molecular biology and cloning techniques, one of ordinary skill in the art would be similarly enabled to clone the gene related to the EST entry for W26469 from GenBank and use that gene to design primers or to produce an antibody.

These arguments are not found persuasive. There is no evidence on the record that W26469 encodes a protein. The EST sequence can be from any part of a transcript, such as the 5' untranslated region, the coding sequence, or the 3' untranslated region. As discussed in the rejection of record, no open reading frame could be found for SEQ ID NO: 36 (e.g., see page 10 of the Office action mailed 6/19/2009). There is no evidence on the record to support the assertion that SEQ ID NO: 36 encodes a protein expressed in renal tissue. One would have no more information than the sequence of SEQ ID NO: 36 and the description in the GenBank entry to rectify the sequence ambiguities present in SEQ ID NO: 36 to enable the measurement of expression levels of mRNA transcribed therefrom or protein encoded thereby. The description provided in the GenBank entry would result in the identification of any sequence expressed in human retina, and not necessarily the sequence of W26469. For these reasons, the correct identity of each nucleotide listed as an ambiguous nucleotide in SEQ ID NO: 36 would not have been obvious to one of ordinary skill in the art at the time the invention was made and would not enable the present invention.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 1-3, 8-11 and 15-18 under 35 U.S.C. 112, first paragraph, Applicant's arguments filed 7/24/2009 have been fully considered but they are not persuasive.

At the last paragraph of page 13, the response notes that the phrase "corresponding levels of expression" has been removed from the claims, rendering this aspect of the outstanding written description rejection moot. This specific argument has been found persuasive. The discussion related to "corresponding levels" has been removed from the rejection.

Ata page 14, paragraph 2, the response asserts that the discussion in the enablement section substantiates that Applicants were in possession of the claimed methods.

These arguments are not found persuasive. The method requires a genus of reagents to detect the expression of the nucleotide sequence of SEQ ID NO: 36, mRNA transcribed therefrom, or protein encoded thereby. If one could envision the sequence of SEQ ID NO: 36 without sequence ambiguities, and that sequence encoded a protein, one would be put in possession of those reagents capable of assaying the expression of SEQ ID NO: 36. However, one cannot envision the sequence of SEQ ID NO: 36 for the reasons of record and the reasons set forth above in response to the arguments directed to the enablement rejection. Therefore, the teachings of the as-filed specification and prior art do not place one in possession of the reagents capable of assaying the expression of SEQ ID NO: 36.

At page 14, paragraph 3, the response asserts that the claims are not directed to product claims and, thus, are not required to provide detail to allow a skilled artisan to envision the gene related to the EST entry for W26469 (SEQ ID NO: 36). The response asserts that one would not need to know the detailed structure of SEQ ID NO: 36 to perform the claimed methods.

These arguments are not found persuasive. The claims are directed to methods that encompass the provision of reagents capable of assaying the expression level of SEQ ID NO: 36. If one does not have the specific sequence of SEQ ID NO: 36 (the actual sequence without ambiguities), one cannot envision the structure of the reagents. Applicants have not provided enough detail such that, when that detail is coupled with the knowledge available to one of ordinary skill in the art, a skilled artisan would understand that at the time of filing of the instant application, Applicants possessed what they now claim. The response does not provide evidence that structures of reagents to detect the expression of mRNA transcribed from SEQ ID NO: 36 or protein encoded thereby were available at the time the invention was made.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Examiner
Art Unit 1636